A concerted appeal for international cooperation in preclinical stroke research

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A Concerted Appeal for International Cooperation in Preclinical Stroke Research

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> Despite dramatic advances in the molecular pathogenesis of disease, translation of basic biomedical research into safe and effective clinical applications remains a slow, expensive, and failure-prone endeavor.
>
> Francis S. Collins1

The global burden of stroke on patients, their relatives, health systems, and the economies that support them is tremendous. In an unprecedented move, the World Health Organization (WHO) and the United Nations have responded to this challenge by declaring the fight against stroke a top priority in their drive to prevent and to control noncommunicable diseases.2 Indeed, great progress has been made in our understanding of stroke pathophysiology. This has led to the development of thrombolysis, a highly efficient therapy for a subset of patients with acute ischemic stroke. We came to realize that the responses of brain tissue to substrate deprivation are complex, and that not only neurons need to be considered but also glial and vascular cells, as well as local or blood-derived cells of the

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immune system.3–5 We now know that ischemia triggers a multitude of endogenous protective mechanisms in the brain which help to contain the ischemic lesion evolution and protect the brain from further damage.6 The brain has a tremendous capacity to overcome functional deficits, and as we begin to understand how brain plasticity works, we are actually finding evidence for tissue repair.7 We are also beginning to appreciate the interaction between the ischemic brain and the other organ systems, such as the immune system,8 the cardiovascular system, or systemic metabolism, a multidirectional signaling with tremendous impact on the outcome of patients with stroke.9 Taken together, research during the past few decades has suggested numerous targets for therapeutic intervention to restore perfusion, block mechanisms of damage, or induce endogenous mechanisms of protection, intercept deleterious signaling to other organs, or to even foster plasticity or repair to recover lost function. Treatment approaches based on this understanding have demonstrated efficacy in a variety of preclinical models of the disease.

However, associated clinical trials have been unable to translate most of these advances into drugs with a clear benefit in patients. Developing new drug treatments for human disease is challenging in any field, and the number of new drugs coming to market continues to fall. Although large numbers of novel treatment strategies are developed in laboratories each year and show beneficial effects in animal models, very few are ultimately proven to be effective in patients.10,11 The stroke field has been particularly affected by the failure to translate drug efficacy in stroke from animal studies to clinical trials.12

The reasons underlying this translational roadblock13,14 are currently being discussed intensely by stroke researchers and in industry and funding agencies worldwide. They are all struggling to develop strategies to overcome the roadblocks impeding the development of effective therapies. For example, the European Commission invited a group of European stroke experts to provide research priorities for attacking this translational roadblock.15 More recently, basic and clinical stroke researchers from North America, Europe, and the Asia-Pacific regions convened in 2 workshops (Barcelona, Spain, May 2011 and Potsdam, Germany, May 2012). The need for international collaboration in cerebrovascular research and therapeutics was also discussed at the meeting of the American Association for the Advancement of Science (Boston, February 2013). Likewise, the Stroke Progress Review Group of the National Institutes of Health (NIH)/National Institute of Neurological Disorders and Stroke (NINDS), recently conducted a 10-year review of the state of stroke research16 and set priorities to shape future NINDS programs and policies focusing on the improvement of bench to beside translation and stressing the importance of research cooperation and research networks. We wish to summarize the background for such cooperation and outline a proposal that might be a first step toward accelerating progress in translational stroke research.

Stroke: A Global Challenge

Worldwide >15 million strokes and 6 million stroke deaths occur per year, and 55 million survivors are experiencing the consequences of a stroke. The costs of stroke are substantial. After adjusting for inflation, it has been estimated that they range in the developed world from US$266 billion to US$1038 billion each year.17 The WHO forecasts a global doubling of these figures by 2030 as the world population ages.18 Although stroke engenders a massive family and societal burden, we unfortunately have few effective therapies. Thrombolysis, because of its short time window, diagnostic requirements, and contraindications, can only benefit a small percentage of stroke patients.19 Stroke units have proven to produce reductions in mortality, institutionalized care, or dependency, but effect sizes and availability are limited.20 This paucity of therapeutic options persists, despite intensive research efforts to develop new effective therapies.

The Problem: Failure to Translate

The translation of animal model research to the stroke patient is best exemplified by the success of reperfusion strategies. There is a wealth of large and small animal experience, and a growing body of work on vascular processes in the central nervous system. It is clear that the location and the extent of ischemic injury begin within the first moments of the vascular occlusion. However, we only partially understand the exact events that ensue from occlusion of a major brain-supplying artery, the brain's attempts to recover from the insult, or the complex interplay of brain, cardiovascular, and immune system before stroke hits and in its wake. A deeper understanding of these mechanisms is a prerequisite for the development of novel treatment strategies that benefit patients, in whom comorbidities and age further complicate pathobiology.

In addition, there is a growing body of quantitative evidence that preclinical stroke research, just as in other areas of biomedicine, has been confounded by quality problems and negative publication bias.11,21,22 Our experimental paradigms are designed to show large treatment effects, and although statistically efficient, they may be clinically less relevant. In view of the difficulties in developing novel and effective therapies for this common and disabling disorder, there is a clear need to rethink the paradigms and dogmas of this research field. Worldwide, researchers and funding agencies have been analyzing potential causes for the translational roadblock. Independently, several common themes have evolved from these discussions (Table 1). One view is that the complexity of the stroke research problem cannot be solved on a local or a national level, and that a transnational effort may be needed to bundle preclinical research capacity and link it to the clinical realm.

Multiple Opportunities

Most experts agree that there is no fundamental reason to believe that reperfusion and treatment in stroke units need to remain the only effective treatment options for patients with ischemic stroke. This optimism is fueled by the observation that numerous examples of preclinical research have parallel examples of improved outcomes in the clinic (Table 2). In addition, opportunities are available for multidisciplinary strategies to generate new knowledge on prevention, mechanisms of injury, plasticity, and repair. The Stroke Progress Review Group has identified and prioritized many scientific research opportunities and medical needs in stroke prevention, treatment, and recovery research.16

Prevention

Technological advances in high throughput genotyping will allow major breakthroughs in the elucidation of the genetics of cerebrovascular risk factors, in particular through Genome-Wide Association Studies46 and exome sequence analysis.47 An important focus will be the prevention of cerebral small vessel disease, a major contributor to age-related cognitive impairment, and a range of agents that might reduce damage to cerebral small vessels in high-risk populations are currently undergoing preclinical testing.48

Treatment

Reperfusion via intravenous thrombolysis has helped to establish the time is brain concept in acute stroke treatment and accomplish major improvements in treatment infrastructure, culminating in the concept of mobile stroke units.49 These studies have paved the way for testing hyperacute (golden hour) treatments, including some previously tested agents, which may have been effective had they been initiated earlier than they were in prior trials. Recent research on endogenous brain protective strategies has led to the discovery of a number of promising treatment strategies that boost such evolutionarily conserved mechanisms.6 Although clinical beneficial neuroprotection has been elusive so far, brain protection in

combination with reperfusion seems logical and carries the potential to increase the benefit of reperfusion by blocking some of its deleterious effects.50 In addition, the efficacy of recanalization and reperfusion may be improved, either by the use of alternative thrombolytics51 or by mechanical devices.52

Recovery and Rehabilitation

The brain can recover function after injury, at least partially. Only recently we have started to understand the mechanisms of this remarkable plasticity and regeneration. This has led to pharmacological strategies to foster recovery, pharmacologically, via cell therapy, rehabilitation measures, stimulation devices, or robotics.53 For example, there is strong evidence that transcranial electric stimulation, in particular, when combined with behavioral practice has beneficial effects on stroke rehabilitation outcomes.54 Likewise, there seem to be exciting opportunities for neuromodulation of stroke recovery through emerging technologies, such as MR-guided focused ultrasound. Biotechnological developments may provide new avenues for fostering endogenous recovery, whereas nanotechnology drug delivery approaches offer novel possibilities for stroke treatment. The remarkable advances in cell therapy for stroke underscore the firm role of this strategy in future research endeavors.

Further opportunities to develop successful strategies to prevent and to treat stroke successfully are emerging from research on the interplay of the various cellular elements of the brain, the neurovascular unit.55 In a paradigmatic shift, the field has realized that a neurocentric view oversimplifies stroke pathophysiology. Since then it has become clear that a complex interaction of endothelial cells, astrocytes, microglia, pericytes, inflammatory cells from the blood, etc, determines the fate of brain tissue after stroke. This research has now exposed numerous new targets for treatment.56

Another transformative area was the investigation of the complex interaction of the injured brain after stroke with peripheral organs,57 in particular, the immune system.58 Complications are a highly important contributor to the morbidity and mortality of stroke, and also a major problem for recovery.59 We are now starting to understand the underlying mechanisms (eg, stroke-induced immunodepression), which increases susceptibility to infection,60) and promising therapies are being developed. It is very likely that ongoing research on the interaction of the brain after stroke with systemic metabolism, the cardiovascular system, the liver, the gut microbiome, etc, will lead us to further therapeutic targets to improve stroke outcome.

All these approaches will be greatly helped by the advances in the identification and validation of biomarkers (blood, imaging61,62) for most relevant stroke subtypes in combination with (epi)genetic and premorbidity phenotyping to predict disease pathophysiology. The ultimate goal of these promising developments is to use transcriptomics, proteomics, as well as immunology, and noninvasive brain imaging (computed tomography, MR, single-photon emission computed tomography, positron emission tomography) to establish diagnostic fingerprints of disease-specific markers to stratify patients in a time and pathophysiological context-dependent manner.

In all these areas, we are only beginning to understand the pathobiological mechanisms, and it is clear that further preclinical research is necessary. Agreement exists that modeling of cerebrovascular disease should include advanced age and comorbidities typical of the human disease, such as diabetes mellitus and hypertension, as well as environmental factors (eg, Fisher et al63). However, because of the overwhelming costs and technical challenges of modeling stroke in aged comorbid animals, most studies have used healthy young animals. This could be overcome by combining the expertise and availability of models and

confounders in a network of international experts, and by providing incentives for crossvalidation within the network.

Thus, numerous possibilities for transnational research cooperation exist that address the problems of fragmentation, limited resources, and the need for multidisciplinary training of new stroke scientists.

Following the example of clinical medicine, in which multinational consortia conduct clinical trials, and some highly effective international cooperation in the preclinical realm (see below), we propose the development of multinational stroke research initiatives. Sharing data and biomaterial in preclinical stroke research, as well as combining research excellence to elucidate novel pathophysiological concepts, and consensus on therapeutic targets, could accelerate translation to clinical trials. This could lead to the establishment of international quality standards with crossvalidation and reproduction of results before decision making on clinical development.64,65

Successful Examples of International Research Collaboration

Research is an international effort and scientists are already collaborating on many individual cerebrovascular research projects. However, scaling up collaborations to the level required to generate the resources and synergies needed requires a structured process. Ideally, such a process can be simultaneously executed by groups of researchers and clinicians (bottom-up) and by funding agencies and scientific societies (top-down) in a coordinated way. An example for a successful bottom up interaction of international scientists is the development of thrombolysis for stroke in the 1980s–2000s, which in its course also led to an improvement in clinical stroke trial expertise. However, a top example of a highly successful structured international research collaboration in biomedicine, is the deciphering of the human genome. We may also learn how to organize and govern multinational research from ongoing international collaborations, such as those in genetics. Triggered by rapid methodological advances in genotyping large numbers of individuals, successful approaches to project selection, data deposition and distribution, collaborative analysis, publication and protection of intellectual property claims on a large, international scale were recently developed (eg, GAIN Collaborative Research Group66), many of which can serve as templates for other fields. Extreme but instructive examples from outside medicine include research collaborations in physics that are focused on experiments using expensive equipment (particle accelerators and detectors, eg, European Organization for Nuclear Research CERN: http://www.cern.org) or on research on matter under extreme conditions of temperature, pressure, or density (eg, Extreme Matter Institute EMMI: http://www.gsi.de/emmi). Apparently, the physics community has established a culture of collaboration that makes possible such highly successful large-scale initiatives and that pervades their entire research operation, including their publication practice (eg, their archive for electronic preprints of scientific papers arXiv:http://www.arxiv.org). We would hope that stroke pathophysiology is easier to decipher than the fundamental physical laws of nature, but we suggest that many lessons can be learned from these other examples of international scientific cooperation, in particular, with respect to organization, upscaling, and governance. Importantly, a strong foundation for development of international stroke research collaborations has been laid by 2 large preclinical research consortia that are currently demonstrating the benefits of sharing results, distributing tasks, and bundling expertise in stroke research. These are the European Stroke Network and the Canadian Stroke Network, which have recently initiated unique pilot collaboration across the Atlantic (Table 3).

Benefits and Added Value

The experience of the European and Canadian Stroke Networks has demonstrated that multidisciplinary expertise can provide high levels of complementarity. Pooling of resources, mutual training opportunities, and exchange of research expertise have served to enhance and accelerate the process of translation. Complex issues can be broken down and distributed in a coordinated fashion between partners. The vast experience of these stroke networks suggests that further benefits could be reaped from enhancement of their previously developed avenues of collaboration. For example,

1. Stroke research data repositories would collect data about results or planned experimental trials and also produce a catalog of models and methods platforms offered by participating centers to the network. In the stroke clinical trial area, such repositories already exist, for example, at the Cochrane Stroke Group (http://stroke.cochrane.org/) or the Virtual International Stroke Trials Archive (http://www.vista.gla.ac.uk/.) Data contained in these repositories have already provided answers to many clinical problems.
2. The use of common standards and data elements (such as NINDS CDEs for clinical stroke research, http://www.commondataelements.ninds.nih.gov/Stroke.aspx) streamlines research, and allows data sharing.
3. Sharing of biomaterials allows the most effective use of precious tissue samples from experimental models and organisms.

In addition to these already existing forms of collaboration in the stroke field, we propose novel forms of interaction:

1. Participating stroke researchers would consent to certain quality standards and common end points and use similar tests to compare and share results (open labs). This would facilitate the free movement of researchers, data sharing (including neutral or negative findings), and exchange of protocols (including feedback/input on methodological difficulties and solutions).
2. Laboratories might organize reciprocal audits and data monitoring, as well as conduct round robin tests.
3. A network of experimental laboratories could organize multicenter trials to replicate key results and perform pivotal trials, or conduct randomized phase III type preclinical trials. These examples are neither complete nor exclusive; various combinations are possible (eg, multicenter trial and common data elements, or common data elements and data repositories).
4. These multicenter studies would be based on well-defined study protocols, including robust sample size calculations, and would be of sufficient scale to deliver the large numbers of animals required to demonstrate smaller, but possibly more clinically relevant, treatment effects.
5. By allowing experiments with a factorial or stratified design (including different strains and/or species, different severity of injury, different comorbidities) the robustness of conclusions of efficacy, and their generalizability, could be increased. 67

Toward Realization of International, Multicenter Preclinical Trials

Bath et al64 and Dirnagl and Fisher65 have called for international, multicenter preclinical phase III-type studies before moving from stroke models to clinical trials. Such phase III preclinical trials would require international participation, thus representing structured

international collaboration in preclinical stroke research. They are not intended to replace basic stroke research targeted at discovering or investigating pathophysiological mechanisms or drugs (preclinical phase I), or initial preclinical trials to demonstrate efficacy by individual scientists (preclinical phase II). Rather, they would be based on such prior studies, and only those compounds or treatment principles that were highly promising in phase I and II would move into phase III. Design elements would include steering and data monitoring committees, robust and clinically relevant outcome measures, use of biomarkers, sufficient statistical power, prespecified primary efficacy end point, as well as hypotheses generating secondary end points, registration in public registry (mandatory for publication in scholarly journals). The complexities of a multicenter multimodal paradigm might indeed be a strength of this collaborative format: the inclusion of centers with various focal cerebral ischemia models may be considered to recreate the heterogeneity of stroke subtypes and the varying severity of this disorder. Various strains (or even species) may be used to mimic patient heterogeneity. Studies could be designed in such a way that they are informative even when the results are neutral or negative. Several international stroke research consortia are currently aiming to develop the capacity to undertake international multicenter animal studies to improve the validity and generalizability of current preclinical research.

A variation of this format may be deduced from the clinical Neurological Emergencies Treatment Trials Network (http://www.nett.umich.edu/nett) of the NIH/NINDS. It is based on the idea that promising new trials of drugs for acute neurological emergencies that are ready for phase III trials should be conducted by sites that have networks of hospitals with active emergency departments that can run clinical trials. In a similar fashion, principal investigators would submit an application for a phase III preclinical trial to a network of collaborating laboratories suitably equipped to conduct high-quality efficacy trials in animals, and the application would undergo peer review. Each site could apply to become a center on the basis of their expertise, commitment to high-quality and rigorous standards, and unique resources. A review or governance committee could decide on the selection of sites on the basis of the overall aims, scope, and goals of the preclinical consortium. Positive results that attest to robust efficacy could then be the benchmark for advancing into clinical trials. The pharmaceutical industry could be approached to support such a network as well and have their treatment platforms deemed appropriate for evaluation by the international preclinical network.

Open Issues

True cooperation, as proposed here, raises a number of issues. First and foremost, the scientific community (researchers, journal editors, scholarly societies) needs to move from reflection (this article) to action. A bottom-up approach in which we share data and consent on quality standards could be the beginning. In parallel, international and national funding bodies, such as the European Commission, the NIH, the Canadian government, the Australian National Health and Medical Research Council, the National Science Foundation of China, etc, need to be convinced of the potential value of such collaborations. Globalization of the scientific endeavor is presently a major charge of many of these organizations, and there are promising signals that specific programs may be initiated in the near future.

Other challenges include intellectual property management, development of structures for mutual project governance, scientific monitoring, effective dialogue for true multidisciplinary involvement beyond neuroscience, and delineation of the role of industrial cooperation. Fortunately, however, previous experience in transnational networks has provided fundamental frameworks for addressing such challenges. Another concern is

authorship of articles generated by the international preclinical network. The example of the physics community and how it has handled this issue is a valuable lesson.

Conclusions

Translational stroke medicine requires renewal, and international collaboration in preclinical research may be an important step to overcome hurdles impeding progress. The tremendous power of international research collaboration has been convincingly demonstrated in physics, and several transnational collaborations have already delivered proof of concept in the stroke field. The experience gleaned from such collaborations is paving the way for an exciting new era in stroke research, which strives to harness the multitude of benefits achievable through international collaboration. Now is the time for concrete action to advance the agenda and establish an international preclinical stroke network.

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Table 1

Lost in Translation—Some Potential Reasons Why Clinical Stroke Trials Were Unable to Replicate Bench Findings

Complexity of ischemic pathophysiology underestimated
Low quality of preclinical studies, underpowered, effect sizes overestimated, results not robust (low internal validity)
Stroke models do not match with patient characteristics (age, sex, comorbidities, polypharmacology; low external validity)
Negative publication bias (particularly in preclinical research)
Heterogeneity of stroke patients, therapies not matched to individual pathophysiology
Super systemic effects (on immune, cardiovascular system, etc) attributable to a substantial fraction of stroke morbidity and mortality, but little understood and under-researched
Timing of therapy wrong or clinically irrelevant, clinical trial design not matched to preclinical findings
Significant species differences

Table 2

Found in Translation—Stroke Models Predict or Parallel Clinical Phenotypes

Pathophysiological concepts	The penumbra concept was developed and refined in animal models of cerebral ischemia, and has proven clinical usefulness	Astrup et al[23]
	Thrombolysis is the only pharmacological treatment of acute ischemic stroke of proven efficacy, is equally efficacious in embolic models of stroke	Zivin et al,[24] The National Institute of Neurological Disorders and Stroke rtPA Stroke Study Group[25]
	Spreading depolarizations and spreading ischemia, first described in animal models, occur in humans and correlate with spread of lesion	Dreier[26]
Treatments	Identical time window for rtPA thromobolysis in rodents and humans	Quartermain et al,[27] Zhu et al,[28] Lees et al[29]
	Hypothermia, a concept originating from and refined in animal models of cerebral ischemia, has entered clinical guidelines to protect the brain after cardiac arrest	Rosomoff,[30] hypothermia after Cardiac Arrest Study Group,[31] Bernard et al[32]
	In mouse and man: increased risk of hemorrhage and BBB disruption in erythropoietin/tPA treatment	Ehrenreich et al,[33] Zechariah et al[34]
	Mouse studies predict outcome of human GPIIb/IIIa receptor antagonist trial	Kleinschnitz et al,[35] Adams et al[36]
	In mouse and man: statin use during stroke is protective, withdrawal is potentially harmful	Gertz et al,[37] Flint et al[38]
	In mouse and man: clinical deterioration after treatment with xenogenic intercellular adhesion molecule-1 antibody (Enlimomab)	Furuya et al[39]; Enlimomab Acute Stroke Trial Investigators[40]
Complications	Weight loss and sarkopenia after stroke: body weight changes after experimental stroke parallel those in humans	Jönsson et al,[41] Scherbakov et al[42]
	Super systemic effects of stroke in animal models are predictive for those effects in humans (eg, immune system and infection)	Prass et al,[43] Urra et al,[44] Vogelgesang et al[45]

BBB indicates blood brain barrier; rtPa, recombinant tissue-type plasminogen activator; and tPA, tissue-type plasminogen activator.

Table 3

Examples of Already Existing Large-Scale/Transnational Cooperations in Preclinical Stroke and Stroke-Related Research

European Stroke Network	A collaborative effort of the European Union's Seventh Framework Program that brings together researchers, government, industry, the nonprofit sector, and patient group associations. It coordinates the research efforts of 29 institutions in 13 countries	http://www.europeanstrokenetwork.eu
Canadian Stroke Network	Established with the help of the Canadian government in 1999. It incorporates >100 researchers at 24 universities at present	http://www.canadianstrokenetwork.ca
InTBIR	A collaborative effort of the European Commission, the Canadian Institutes of Health Research and the National Institutes of Health. In July the European Commission 2012 issued a call (HEALTH. 2013.2.2.1-1) to support InTBIR with ≤30 Mio	http://ec.europa.eu/research/health/medicalresearch/brain-research/internationalinitiative_en.html
Transatlantic networks-Fondation Leducq	Transatlantic Networks of Excellence in Cardiovascular and Neurovascular Research. The program awards grants of up to US $6 000 000 over 5 years to collaborative	http://www.fondationleducq.org

	teams of European and North American scientists, allowing researchers to take advantage of the strengths and resources on both sides of the Atlantic	
SIRIUS: Sustained Investigation of Recovery and Immunologic response after stroke Using neural Stem cells	The Department of Neurosurgery of the Stanford University and the Translational Center for Regenerative Medicine (University of Leipzig) collaborate to assess safety and efficacy parameters of allogeneic stem cell therapy for stroke in a large animal species before entering a clinical trial. Supported by national funding agencies (the California Institute for Regenerative Medicine and the German Ministry for Education and Research)	http://www.trm.uni-leipzig.de/en/research/sirius/research-project-sirius/r-sirius-a-1184.html

InTBIR indicates International Initiative for Traumatic Brain Injury Research.